B. Amendment to the Claims

Please amend claims 1, 16, 24, 25, 27 and 28 as follows. A listing of all claims is provided.

1. (Currently Amended) A method for screening of the presence or absence of variation in a portion of a sample nucleic acid comprising the steps of:

(a) providing a DNA array substrate by:

i) preparing a substrate;

ii) preparing a group of probes, each probe having a base sequence that hybridizes with a wild-type sequence of the portion to give a strong signal;

iii) preparing a group of probes, each probe having a base sequence that is expected to hybridize with a gene variant but not with the wild-type sequence to give a strong signal, the group not containing any probes of the group prepared in ii); and

iv) fixing each probe on the substrate as a separate probe spot in such a manner that probe spots of each group are arranged in one region on the substrate different from a region in which the probe spots of other groups are arranged and the probe spots are grouped such that each said region contains probes not found in other regions;

(b) reacting the sample nucleic acid with the probes on the DNA array substrate;

(c) measuring a signal intensity of each region as a total of signals originating from respective hybrids formed between the sample nucleic acid and the probes to obtain a histogram pattern of signal intensity of the regions; and

(d) determining the presence or absence of mutation in the sample nucleic acid comparing with the histogram pattern with a histogram pattern obtained using an array substrate obtained by step (a) and a reference nucleic acid having the wild-type sequence.

2. (Previously Presented) The method according to claim 1, wherein the signal is a light and a total light quantity emitted from each region is measured as the signal intensity.

3. (Original) The method according to claim 2, wherein the light is fluorescence.

4. (Original) The method according to claim 2, wherein the light is a chemical luminescence.

5. (Previously Presented) The method according to claim 1, wherein the steps (a-iv) to (d) further comprise:

(a-iv) preparing separate regions on a substrate by fixing probes on a surface of the substrate, wherein the separate regions comprise:

a first region containing probes which provide a signal of a certain intensity on reaction with a reference nucleic acid having the wild-type sequence,

a second region containing probes which provide weaker signals on reaction with the reference nucleic acid, and

a third region containing probes which do not form hybrids on reaction with the reference nucleic acid;

(b and c) reacting the DNA array of step (a) with the reference nucleic acid and measuring a signal of at least one region selected from the three regions to obtain a first pattern;

(b' and c') reacting the DNA array of step (a) with the sample nucleic acid and measuring a signal of at least one region corresponding to the at least one region selected in step (b and c) to obtain a second pattern; and

(d) determining the presence or absence of variation in the sample nucleic acid by comparing the first and second patterns.

6. (Previously Presented) The method according to claim 5, wherein the at least one region selected in step (b and c) is the first region giving a strongest total signal and/or the third region giving no or a weakest signal on reaction with the reference nucleic acid.

7. (Previously Presented) The method according to claim 5, wherein the separate regions are arranged on the substrate in order of signal intensity along a direction of a detection, wherein the signal intensity is obtainable on a reaction with the reference nucleic acid.

8. (Previously Presented) The method according to claim 5, wherein the at least one region selected in step (b and c) is the third region and the sample nucleic acid is determined to have variation when the signal is detected in the third region with the sample nucleic acid in step (b' and c').

9. (Cancelled)

10. (Previously Presented) The method according to claim 5, wherein the at least one region selected in step (b and c) are both the first and the third region and determining the presence or absence of variation is determined by comparing the ratio of the intensity of the third region to that of the first region.

11. (Previously Presented) The method according to claim 5, wherein all three regions are selected in step (b and c) and the presence or absence of variation is determined by comparing the histogram pattern of signal intensity.

12. (Original) The method according to claim 5, wherein detection of the total signal is performed by an area sensor.

13. (Original) The method according to claim 7, wherein detection of the total signal is performed by a line sensor.

14. (Previously Presented) The method according to claim 1, wherein a base length of the probes is 8 to 30 nucleotides.

15. (Previously Presented) The method according to claim 14, wherein the base length of the probes is 12 to 25 nucleotides.

16. (Currently Amended) A DNA array substrate for screening variation in a portion of a nucleic acid comprising:

a first group of probes, each probe having a base sequence that hybridizes with a wild-type sequence of the portion to give a strong signal, and

a second group of probes, each probe having a base sequence that is expected to hybridize with a gene variant but not with the wild-type sequence to give a strong signal;

wherein each probe is fixed as a separate probe spot on a substrate to form at least two separate regions of probe spots selected from:

a first region containing probes of the first group,

a second region containing probes of the second group, each of which provides a weaker signal than the probes of the first region on reaction with the wild-type sequence, and

a third region containing probes of the second group, each of which provides no signal on reaction with the wild-type sequence,

wherein the probe spots are grouped such that each one of the regions contains probes not found in other regions.

17. (Original) The DNA array substrate according to claim 16, wherein the signal is fluorescence.

18. (Original) The DNA array substrate according to claim 16, wherein the signal is chemical luminescence.

19. (Cancelled)

20. (Previously Presented) The DNA array substrate according to claim 16, wherein the separate regions are arranged on the substrate in order of signal intensity obtainable by reacting with the wild-type sequence along a direction of a detection.

21. (Previously Presented) The DNA array substrate according to claim 16, wherein a length of the probes is 8 to 30 nucleotides.

22. (Previously Presented) The DNA array substrate according to claim 21, wherein the length of the probes is 12 to 25 nucleotides.

23. (Original) A system for detecting variation comprising a DNA array substrate according to claim 16 and a signal measuring apparatus which measures signals from separate regions of the DNA array substrate.

24. (Currently Amended) A method for detecting the presence of a target nucleic acid in a sample using an array substrate having plural probe spots arranged thereon to form an array, wherein said probe spots are arranged into groups such that each group contains probes not found in other groups ~~and wherein spots in each of said groups have bonded probes different in sequence from probes bonded to spots in other said groups~~, the method comprising the steps of:

a) measuring a total signal intensity of a plurality of the probe spots integrally wherein the probes are in a hybridized state;

b) preparing a histogram of the total signal intensities obtained by repeating the step a) for the remaining spots; and

c) determining the presence of the target nucleic acid on the basis of the histogram pattern.

25. (Currently Amended) A method for detecting the presence of a target nucleic acid in a sample using an array substrate having plural probe spots, wherein said probe spots are arranged into groups such that each group contains probes not found in other groups ~~and wherein spots in each of said groups have bonded probes different in sequence from probes bonded to spots in other said groups~~, and the spots are grouped into two or more groups of two or more spots, the method comprising:

a) measuring a total intensity of signals emitted from the probes for each group wherein the probes are in a hybridized state;

b) preparing a histogram of signal intensities of the groups to obtain a pattern; and

c) determining the presence of the target nucleic acid on the basis of the histogram pattern.

26. (Previously Presented) The method according to claim 25, wherein the groups comprise at least a first group and a second group, the signal intensity of the first group is strongest in hybridization with a first target nucleic acid, and the signal intensity of the second group is strongest in hybridization with a second target nucleic acid.

27. (Currently Amended) An array substrate for determining the presence or absence of a target nucleic acid in a sample, the array substrate comprising:

a substrate;

probe molecules; and

a plurality of spots of probes arranged on the substrate in an array form,

wherein the probe molecules are the same in one probe spot and different between probe spots, and the probe spots are divided into plural regions, grouped such that each region contains probes not found in other regions, and each region corresponds to one of target nucleic acids different in their sequence.

28. (Currently Amended) An array substrate for determining the presence of at least one of a first target nucleic acid and a second target nucleic acid in a sample, the array substrate comprising:

a substrate;

probe molecules; and

a plurality of spots of probes arranged on the substrate in an array form,

wherein the probe molecules are the same in one probe spot and different between probe spots, grouped such that each region contains probes not found in other regions, and the probe spots are grouped into groups of at least two or more probe spots, the first group is expected to give a stronger integral signal intensity in hybridization with a first target nucleic acid than with a second target nucleic acid, and the second group is expected to give a stronger integral signal intensity in hybridization with the second target nucleic acid than with the first target nucleic acid.